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EDITORIAL COMMENT

The Coming of Age of Natriuretic Peptides

The Emperor Does Have Clothes!*

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Since its approval by the Food and Drug Administration in November 2000, the worldwide uptake of natriuretic peptides (NPs), both in the clinical and research arenas, has been nothing short of astounding. In the U.S. alone, recent College of American Pathology (CAP) surveys suggest that approximately 83% of hospitals use some type of NP testing. Although NP testing was originally focused on rapid diagnosis of patients presenting to the emergency department with shortness of breath, clinicians regularly look to NPs for diagnosing minimally symptomatic or asymptomatic left ventricular (LV) dysfunction, monitoring therapy of patients hospitalized for heart failure, and using NP levels in clinic to help ascertain when decompensation is present. In addition, the importance of B-type natriuretic peptide (BNP) in as a prognostic marker cannot be overstated. In fact, in a population-based prospective community study in Copenhagen, measurements of NPs were stronger predictors for cardiovascular disease and death than was C-reactive protein (1).

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With the widespread popularity of NPs, clinicians have voiced concern over which NP test to use; how to account for differences in age, gender, and renal function; and how best to integrate NP testing into their daily clinical practice. The study by Richards et al. (2) in this issue of the *Journal* goes a long way to help sort out these issues. These investigators are considered one of the world's leading investigators in the use of NPs, compared BNP with NTproBNP in more than 1,000 patients with stable ischemic heart disease. These two peptides are derived from the 134-amino-acid precursor prepro BNP. Upon stimulation of a number of triggers, including wall stretch, ventricular dilation, and/or increased pressures, a 26-amino-acid signal peptide sequence is cleaved from the precursor's N-terminus to produce proBNP. This hormone is further cleaved by a membrane-bound serine protease (corin) into the inactive N-terminal fragment and the active BNP fragment. The authors demonstrated that both peptides were closely correlated to each other and exhibited parallel changes across broad ranges of age, renal function, and LV ejection fraction. The two peptides performed similarly in the detection of ejection fractions reduced below 20%, 40%, or 50% in both symptomatic and asymptomatic patients and were indistinguishable in their ability to predict 12-month all-cause mortality and/or readmission with heart failure.

Thus, it appears that both NPs offer considerable value to the clinician. The findings of this study suggest that the final decision as to which biomarker, BNP or NTproBNP, will be used will not necessarily be based on the differences between the two peptides, but rather the presence of the pre-existing laboratory equipment necessary to run the assay, as well as the perceived need for point-of-care devices versus large laboratory platforms. One thing can be said with certainty in this regard. Although Richards et al. (2) have shown that the two peptides correlate highly, they are not interchangeable; in other words, it would be dangerous for a hospital laboratory to switch from running BNP to NTpro BNP or vice versa without first making sure that the clinicians using the test were aware of the differences, especially in terms of absolute values, because NTproBNP tends to be about 10-fold higher than BNP. In the U.S., about 80% to 90% of current NP testing involves BNP (CAP surveys), whereas in Europe NT proBNP testing is more commonly used (percentages not available). Because BNP was the first peptide to be clinically available, experience with its use as well as the development of accepted algorithms have accounted for its increased use in the U.S. However, with the recent work by Januzzi et al. (3), along with the publication of the PRIDE study, workable clinical algorithms for NTproBNP are being developed.

There are several limitations in this study that should be commented on. The first is that these patients were stable and, as such, strong correlations between the two peptides may not hold in the unstable, acutely presenting patient. For example, NTproBNP levels can rise in acutely ill patients (especially those who are older and have renal dysfunction) to extremely high levels of >30,000 pg/ml. Present studies are focusing on this issue, and algorithms are being developed that help to risk stratify patients with these high levels.

Additionally, the issues of age and gender may not be as important in diagnosing congestive heart failure (CHF) in the acutely dyspneic patient. A substudy of the Breathing Not Properly Trial examined the impact of age, race, and gender and found that if one assumes that failing to treat cases of CHF is worse than treating negative cases (false negatives have more of an impact than false positives), the cut point should not rise higher than 100 pg/ml, even though specificity in older patients might be less (4).

A second limitation in the present study is no fault of the authors, but comes with the territory of large correlative studies: although NP data correlate across a large spectrum of renal function or ejection fractions, what does a single NP

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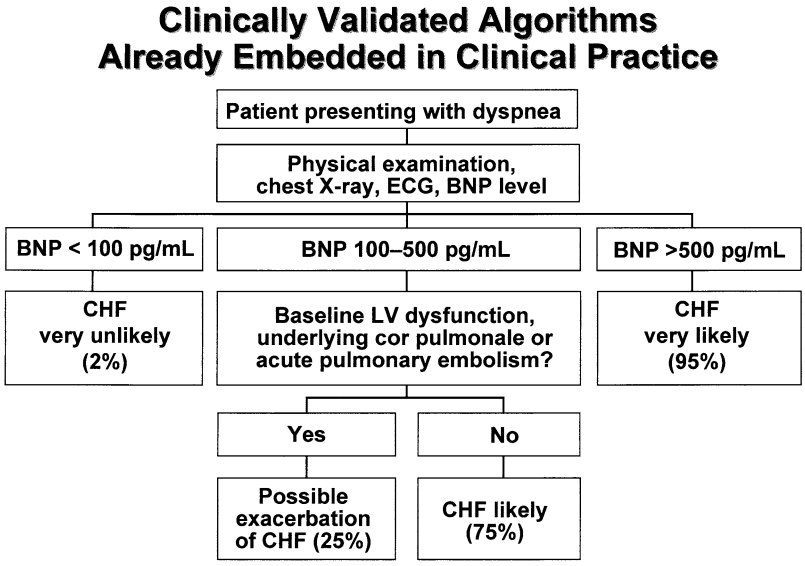

Figure 1. Clinically embedded algorithm for using B-type natriuretic peptide (BNP) levels in the acute dyspneic patient. ECG = electrocardiogram; CHF = congestive heart failure; LV = left ventricular. Adapted from Maisel A. Rev Cardiovasc Med 2002;3:S13.

level at a single place and time in a given patient mean in the real world? For instance, with regards to ejection fraction, several factors could affect a single NP level (other than gender, age, and renal function).

NPs from LV versus right ventricle (RV). Although a normal RV accounts for small amounts of NP secretion, in the setting of pulmonary hypertension the RV can secrete NPs in amounts that correlate to extent of RV dysfunction (5). Many patients with "gray-zone" BNP levels (100 to 500 pg/ml) fall into the category of patients with prior lung disease such as cor pulmonale, whose BNP level is evidence of RV stretch.

Diastolic dysfunction. A number of studies (6,7) have made it clear that in patients with established systolic dysfunction, concomitant diastolic dysfunction will raise NP levels in proportion to severity, with restrictive filling pattern leading to the greatest increase.

Valve disease. A number of recent studies (8,9) demonstrate that valvular diseases such as aortic stenosis and mitral regurgitation may present with elevated NP levels, which may be important in timing of valve replacement. In fact, Richards et al. (2) have demonstrated that for any degree of LV dysfunction, BNP levels will be correspondingly higher, with worsening degrees of mitral regurgitation.

"Wet versus dry." Any NP level must be interpreted in light of whether the patient is at optimum volume status (i.e., euvolemic). Even patients with mild LV impairment and low-normal NP levels will have marked increases in NP levels with decompensation. With interceding conditions such as volume overload, ischemia, or atrial fibrillation, NPs will rise without a change in ejection fraction.

Variability of measurements. Although current NP assays offer precision that ranges from 4% to 12%, this alone does not account for apparent variability of NP. In a limited number of patients, Wu et al. (10) found variability near 100% for both assays. More work is being done in this area to assess the influence of diurnal variation, diet, time of medication, and so forth.

Integrating NPs into practice. ACUTE DYSPNEA IN THE EMERGENCY DEPARTMENTS. Trials such at the Breathing Not Properly multinational study (11) have helped to establish the framework for using BNP in the clinical setting. Figure 1 is an easy-to-follow popular clinical algorithm for using BNP based on data from that study. Figure 2 shows an algorithm for using NTproBNP for evaluation of suspected acute CHF based, in large part, on the recent PRIDE study by Januzzi et al. (3).

Natriuretic peptides also should be useful in triaging patients with CHF in the emergency department. The Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT) (12) demonstrated a disconnect between the perceived severity of CHF cases by emergency physicians and severity as determined by BNP levels. B-type natriuretic peptide levels were far more significant with regards to outcomes than was physician perception of severity, and patients admitted with CHF with BNP levels <200 pg/ml appeared to have no advantage in being admitted.

SCREENING FOR LV DYSFUNCTION. Recent studies have demonstrated that NPs are an important cost-effective tool to diagnose LV dysfunction, either in conjunction with an echocardiogram or, in certain patients, in lieu of echocardiography (13,14,15). One of the great contributions of Richards et al. (2) is specific thresholds for both peptides that the practicing clinician can use in detecting LV dysfunction in stable ischemic heart disease patients. With regards to BNP, our own data are in strong agreement with Richards et al. (2), as we found that BNP levels in the range of 40 to 70 pg/ml allow us to detect echo abnormalities in patients with a high prevalence of disease but who are

"Rule in"

Age strata	Optimal cut-point	Sensitivity	Specificity	PPV	NPV	Accuracy
All <50 years (n=183)	450 pg/ml	97%	93%	76%	99%	95%
All 50-75 years (n=554)	900 pg/ml	90%	82%	82%	88%	85%
All >75 years (n=519)	1800 pg/ml	85%	73%	92%	55%	83%
Overall average		92%	84%	86%	66%	93%

"Rule out"

	Optimal cut-point	Sensitivity	Specificity	PPV	NPV	Accuracy
Rule out	300 pg/ml	99%	62%	55%	99%	83%

Figure 2. Optimal cut points for NTproBNP for diagnosing acute congestive heart failure. The cut points listed in the figures are for acute congestive heart failure diagnosis only. NPV = negative predictive value; PPV = positive predictive value. Adapted from Januzzi JL, et al. Am J Cardiol 2005;95:948–54 (3).

asymptomatic. In addition, we recently found that if we move the cut point even lower, to 20 pg/ml, we can find a group of patients who are very unlikely to have significant ventricular dysfunction (particularly systolic) during subsequent echocardiography. To this end, we have published an algorithm that may be useful for screening in the outpatient setting (16) (Fig. 3).

MANAGEMENT OF CHF. Though not yet a Food and Drug Administration-approved indication, the use of NPs for monitoring volume status and treatment in patients admitted for CHF is promising. The fact that NPs have short half-lives (20 min for BNP, 120 min for NT proBNP) and easy-to-measure levels and are surrogates for wedge pressure, volume, New York Heart Association functional class, and prognosis suggests their usefulness in this setting. Last year, a consensus panel met regarding the use of NPs (17). Although BNP was mainly discussed, many of the consensus conclusions may apply to NTproBNP as well. The following are three consensus statements with regard to BNP levels in the hospital:

- Although in a given patient, BNP level does not always correlate to wedge pressure, in a patient admitted with

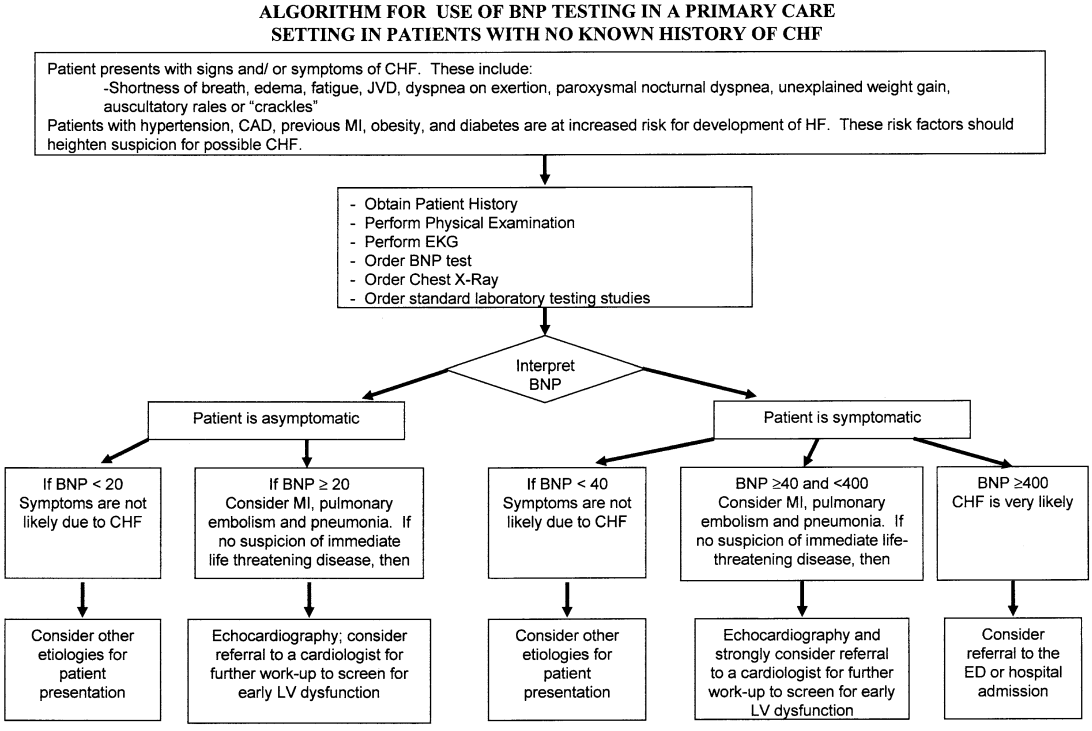

Figure 3. Algorithm for using B-type natriuretic peptide (BNP) testing in the primary care setting. CAD = coronary artery disease; CHF = congestive heart failure; ED = emergency department; EKG = electrocardiogram; HF = heart failure; JVD = jugular venous distension; LV = left ventricular; MI = myocardial infarction. Adapted from Silver et al. (17).

heart failure, high filling pressures secondary to volume overload, and a high BNP level (decompensated or "wet" BNP), a treatment-induced decrease in wedge pressure will almost always be associated with a rapid drop in BNP levels as long as the patient is maintaining adequate urine output.

- Levels of BNP do not need to be drawn every day that a patient is in the hospital. Rational use of BNP levels would be on admission, after a major treatment effect (usually after 24 h of treatment), and when discharge is contemplated (and euvolemia reached).
- Failure of BNP levels to decrease during hospitalization is a poor prognostic sign, suggesting consideration of more intensive monitoring, treatments, and follow-up.

Conclusions. In just five short years, NP levels have permeated not just emergency medicine and cardiology, but have generated interest among those involved in internal medicine, family medicine, and pediatrics. As typically happens in science, the explosion of emerging knowledge often outstrips practitioners' ability to integrate data into their personal infrastructure of clinical practice. Natriuretic peptides are not stand-alone tests. Much as troponin testing must take into account the clinical features of acute coronary syndrome as well as electrocardiographic findings, NP measurements need to be evaluated in concert with a careful history, physical exam, and other laboratory tests to obtain maximum benefit. There is clearly a learning curve for using NP levels. Articles that elevate the knowledge base considerably, such as that of Richards et al. (2), as well as routine use of these peptides in our practice, ensure that our learning will be complete.

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